PATENT SPECIFICATION

NO DRAWINGS

Inventors: THOMAS MARVEL SHARP and WILLIAM SOLOMON

868,552

Date of filing Complete Specification (under Section 3(3) of the Patents Act 1949): Nov. 21, 1958.

Application Date: Dec. 3, 1957. *No. 37608/57.*

Application Date: Sept. 24, 1958. *No. 30546/58.*

Complete Specification Published: May 17, 1961.

Index at acceptance:—Classes 2(3), C1F4(A2: C4: D2: D3: F2: F3: F5), C2B(18: 20: 38); and 81(1), B(1S: 2S).

International Classification:—C07c, d. A61k.

COMPLETE SPECIFICATION

Improvements in or relating to Novel Amidines and the preparation thereof

ERRATA

SPECIFICATION NO. 868,552

Page 1, line 21 and Page 7, line 9, *for* "N" *read* "N'"

Page 2, line 111, *for* "preesnt" *read* "present"

Page 3, line 72, *for* "oxybenzoamidine" *read* "oxybenzamidine"

Page 4, line 19, *for* "aminodecylbenzonitrile" *read* "aminodecyloxybenzonitrile"

Page 5, Examples 17 and 18, *for* "$^7C_{18}$" *read* "C_{18}"

Page 7, line 92 *and* Page 12, line 3, *for* "N" *read* "N".

Page 9, line 6, *for* "18.5" *read* "128.5"

Page 12, line 49, *for* "cyano" *read* "cyano"

Page 12, line 78, *for* "millilitres" *read* "millimetres"

Page 13, Example 3, *for* "N_3, H_2" *read* "N_3O, H_2"

THE PATENT OFFICE,
1st November, 1961

DS 97145/1(82)/R.153 200 10/61 PL

group or a halogen atom, or is a 2:6-naphthylene group.

The compounds of formula (I) have been found active against infections of amoebiasis in experimental animals. Preferred compounds are *p* - 10 - diethylaminodecyloxybenzamidine, 3 - methyl - 4 - 10^1 - diethylaminodecyloxybenzamidine and 6 - 7^1 - diethylaminoheptylphonate) in the presence of ammonia.

The conversion may also take place by the reaction of a compound of formula (II) with an alkali metal amide (such as sodamide) in the presence of ammonia.

In another method a compound of formula (II) is reacted with ammonia or urea in the presence of an inorganic condensing agent such

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International Classification:—C07c, d. A61k.

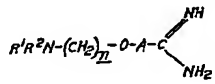
COMPLETE SPECIFICATION

Improvements in or relating to Novel Amidines and the preparation thereof

We, THE WELLCOME FOUNDATION LIMITED, a British Company of 183—193, Euston Road, London, N.W.1, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to amidines and the preparation thereof.

According to the present invention in one aspect there are provided novel amidines of the general formula (I) and their acid addition salts.



(I)

In this and succeeding formulae:—

R^1 and R^2 are the same or different and each is a hydrogen atom or an aliphatic hydrocarbon radical containing from 1 to 4 carbon atoms, or

the group R^1R^2N— is a piperidino, pyrrolidino, morpholino, piperazino, or N^1-benzhydrylpiperazino group;

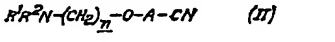
n is an integer from 7 to 12; and

A is an arylene group and is a 1:4-phenylene group which may be substituted in the positions *ortho* with respect to the alkylene-oxyl chain with a methyl or methoxyl group or a halogen atom, or is a 2:6-naphthylene group.

The compounds of formula (I) have been found active against infections of amoebiasis in experimental animals. Preferred compounds are *p* - 10 - diethylaminodecyloxybenzamidine, 3 - methyl - 4 - 10^1 - diethylaminodecyloxybenzamidine and 6 - 7^1 - diethylaminoheptyloxy - 2 - naphthamidine, and their acid addition salts.

The compounds of formula (I) may be prepared by a number of synthetic routes and methods which are all well known and understood in the art. Any such method may be employed in the preparation of the compounds of the present invention. The word "known" is to be understood as designating synthetic routes and methods in actual use or described in the literature on the subject.

According to the present invention in another aspect, the compounds of formula (I) are prepared by converting the cyano group of a compound of the general formula (II) into an amidine group by methods well known *per se* for such a conversion.



(II)

For example, the cyano group may be converted to an amidine group by the reaction of a compound of formula (II) with an alcohol to give an imino ether, followed by the reaction of the latter with ammonia or an ammonium salt.

Another method of conversion comprises the reaction of a compound of formula (II) with ammonium thiocyanate or an ammonium arenesulphonate (such as the benzenesulphonate) in the presence of ammonia.

The conversion may also take place by the reaction of a compound of formula (II) with an alkali metal amide (such as sodamide) in the presence of ammonia.

In another method a compound of formula (II) is reacted with ammonia or urea in the presence of an inorganic condensing agent such

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as aluminium chloride, zinc chloride, ferric chloride or stannic chloride.

In the full synthesis of the compounds of the present invention the sodium salt of a hydroxy nitrile of the formula HO—A—CN is condensed with an excessive proportion of an α:ω-alkylene dibromide and the resulting ω-bromoalkoxy nitrile (which may be largely separated from the α:ω-bis-*p*-cyanoaryleneoxyalkane which is also formed by taking advantage of its relatively greater solubility in ether) can be brought into reaction with an amine of the formula R^1R^2NH. The ω-amino- or substituted ω-aminoalkoxynitrile produced may then be converted into the corresponding amidine, which is the desired product, by any of the methods known *per se* as described above. Usually the product is best obtained in the form of its sulphate salt.

The compounds of the present invention may be presented in any suitable pharmaceutical preparation such as tablets, capsules, suppositories, a suspension in syrup or oil, or an aqueous suspension containing if desired a suitable suspending agent.

According to yet another aspect of the present invention there are provided pharmaceutical preparations comprising an aminoalkoxy - arylene amidine or its acid addition salt as defined above together with an acceptable carrier therefor. Such preparations are conveniently made in unit dosage form, and may be made by any of the methods well known to the art of pharmacy.

The invention will now be described by reference to the following Examples, in which all temperatures are given in degrees Centigrade.

EXAMPLE 1.

A solution of one molecular equivalent of *p*-hydroxybenzonitrile (110 grammes) in a mixture of alcohol (2250 millilitres) and water (350 millilitres) is treated with one molecular equivalent of sodium hydroxide (36.9 grammes) and 1.99 molecular equivalents of 1:10-dibromodecane (550 grammes) and boiled under a reflux condenser during 6 hours. After removing nearly all the alcohol on a steam-bath under diminished pressure, the residue is treated with water and extracted with 3 litres of ether. The extract is dried over anhydrous sodium sulphate, and, upon removing the solvent by evaporation, furnishes a residue which may be subjected to distillation at a pressure of 2.5 millimetres of mercury until the vapour temperature rises to 200°. The resulting distillate, which contains the unreacted excess of the decamethylene dibromide together with products derived therefrom by condensation with the reaction medium, serves for the regeneration and recovery of decamethylene dibromide which may then be used again. The distillation residue which is a solid material weighing 201 grammes is found by elementary analysis to contain 20.2 per cent of bromine. It contains the *p* - 10 - bromodecyloxybenzonitrile, which is the main product of the operation, as well as some 1:10 - bis - *p* - cyanophenoxydecane which is also formed. The latter substance is a solid, sparingly soluble in ether and insoluble in an aqueous medium; while the greater part of it is out of solution and may be filtered out before or during the ether extraction (or it may be ignored), some, nevertheless, finds its way into the ethereal extract and of this, some is deposited on the drying agent and may be filtered out with it. But some proportion of this compound is always found dissolved in the dried ethereal liquid and is for this reason present as an impurity in the *p*-10-bromodecyloxybenzonitrile prepared as described above. However, for the purpose of this invention, the material which weighs 201 grammes and contains 20.2 per cent of bromine is sufficiently pure and may be submitted to the next stage of the process in the condition described. For this purpose it may be dissolved in alcohol (500 c.c.), treated with diethylamine (100 c.c.) and this solution boiled under a reflux condenser during 6 hours. The only basic substance formed in this reaction is that produced by the condensation of the diethylamine with the *p* - 10 - bromodecyloxybenzonitrile. The impurity aforementioned does not react and is not basic in character; it may therefore now be eliminated by methods which are well understood. Thus, after evaporating most of the alcohol and unreacted excess of diethylamine upon a steam-bath under diminished pressure, the residue is treated with water, with an excess of a solution of a caustic alkali and is extracted with one and one-half litres of ether. The product of the reaction, *p*-10-diethylaminodecyloxybenzonitrile, is withdrawn from the ethereal solution by means of dilute aqueous hydrochloric acid. (The remaining ethereal solution so bereft of its basic solute furnishes 34 grammes of a non-basic impurity). The *p*-10-diethylaminodecyloxybenzonitrile hydrochloride now preesnt in dilute aqueous acid solution may be crystallised forthwith, or, it may be further purified by a renewed transference to ether with the aid of an alkali followed by a return to aqueous hydrochloric acid; or, it may be purified in the condition of base by a process of distillation in a vacuum when a small amount of a higher boiling impurity may be eliminated. The *p*-10 - diethylaminodecyloxybenzonitrile hydrochloride so obtained is finally recrystallised from acetone when it constitutes a white crystalline solid weighing 128.5 grammes and melting at 75—85°. It is very soluble in water, in the common alcohols and in hot but not in cold acetone.

Throughout the succeeding operations, during which the nitrile just described is converted to the corresponding amidine, rigorously anhydrous conditions (achieved with the aid of

well-known and customary devices) are observed.

A solution of dry *p*-10-diethylaminodecyloxybenzonitrile hydrochloride (95 grammes) in absolute ethyl alcohol (100 millilitres) is placed in a trough of water (so as to prevent the temperature from rising above about 20°) and saturated with dry hydrogen chloride gas. After standing for 24 hours at the temperature of the room, all volatile matter is removed by suction, the temperature being prevented from falling unduly by immersion in a trough of water at 20°. The residue, which is a gum weighing 130 grammes and showing an incipient tendency to crystallise, is dissolved in 100 millilitres of absolute ethyl alcohol, cooled to a temperature of +5° and mixed with 400 millilitres of a solution (whose temperature is likewise at +5°) obtained by saturating absolute ethyl alcohol kept at 20° with anhydrous ammonia gas. The resulting liquid, which contains a white crystalline solid uniformly suspended therein, is saturated with dry ammonia gas under the conditions already prescribed. After standing at 20° for 65 hours, nearly all volatile matter is removed by suction at 20°. The residue is then treated with 2½ litres of water charged with a large excess of a caustic alkali and extracted with one litre of ether. After drying over a suitable drying agent such as anhydrous sodium sulphate, most of (but not all) the ether is removed from the filtered liquid by evaporation upon a steam-bath. Complete elimination of the solvent is achieved at room temperature by suction under suitable conditions: it is of course not now necessary to observe in all rigour the fully anhydrous conditions hitherto imperative, but suitable precautions are nevertheless taken to prevent an excessive amount of dew being deposited upon the product at this stage. In this way there is obtained a soft, white, crystalline solid which weighs 95 grammes and is *p* - 10 - diethylaminodecyloxybenzamidine. It is converted to the sulphate salt whose composition is $C_{21}H_{37}N_3O,H_2SO_4$ by means of a suitable solution containing 25.5 grammes of H_2SO_4. This salt is crystallised and may be recrystallised from a mixture of water (40 millilitres) and absolute ethyl alcohol (300 millilitres). The first crop weighs 92 grammes, and a further 25 grammes of not greatly inferior material can be recovered from the mother-liquor in a series of additional crops. The salt melts at 224—229° with decomposition. It is very soluble in water but almost insoluble in dry alcohol and other organic solvents.

EXAMPLE 2.

p - 10 - Diethylaminodecyloxybenzonitrile hydrochloride, prepared according to the method described in Example 1, (1.5 g.), and ammonium thiocyanate (1.5 g.) are melted together and heated with stirring to 150° while a stream of dry ammonia is passed in. The temperature is then raised to 180° and maintained for 2 hours. The product is shaken with water, sodium hydroxide and ether, the ether removed and the residue dissolved in absolute alcohol and converted to sulphate with dilute sulphuric acid. *p*-10-Diethylaminodecyloxybenzoamidine sulphate crystallizes, melting point 228—9°, identical with the compound described in Example 1.

EXAMPLE 3.

p - 10 - Diethylaminodecyloxybenzonitrile benzene sulphonate (2.5 g.) and ammonium benzene sulphonate (2.5 g.) are heated and stirred in a current of dry ammonia for 4 hours at 200°. The product is extracted with 30 c.c. of hot water and after cooling filtered from some unreacted *p*-10-diethylaminodecyloxybenzonitrile benzene sulphonate. The aqueous filtrate is made alkaline with sodium hydroxide solution and extracted with ether. The ether is evaporated and the residue converted to sulphate as in Example 1. *p* - 10-Diethylaminodecyloxybenzamidine sulphate is obtained in white crystals melting point 230° identical with the product obtained in Example 1.

EXAMPLE 4.

To *p* - 10 - diethylaminodecyloxybenzonitrile (2.2 g.) in dry xylene (10 c.c.) is added sodamide (2.6 g.) finely powdered under xylene (10 c.c.). The mixture is stirred and boiled under reflux for 6 hours in a stream of dry ammonia. The product which consists of a gelatinous suspension is poured into water; it forms a milky liquid which is acidified with dilute hydrochloric acid. The liquid clears forming two layers which are separated. The aqueous layer is basified with sodium hydroxide and extracted with ether. The ether on evaporation leaves behind *p*-10-diethylaminodecyloxybenzamidine which is characterized by conversion to the sulphate melting point 228—9°.

EXAMPLE 5.

p - 10 - Diethylaminodecyloxybenzonitrile hydrochloride (1.9 g.) is mixed with urea (11.4 g.) and heated in an oil-bath to 150°; anhydrous aluminium chloride (0.67 g.) is then added in portions. A vigorous reaction takes place and when this has subsided the temperature is raised to 190° for one and a half hours. On cooling a horny mass is obtained which is converted to a milky suspension with 150 c.c. of hot water. The suspension is acidified, centrifuged to remove aluminium compounds, made alkaline and extracted with ether to obtain the *p* - 10 - diethylaminodecyloxybenzamidine, characterised by conversion to sulphate melting point 227—230° and identical with that obtained in Example 1.

EXAMPLE 6.

A solution of 3 - methyl - 4 - hydroxybenzonitrile (13.3 grammes) sodium hydroxide (4.0 grammes) and 1:10 dibromodecane (60.0 grammes) in 440 millilitres of 86 per cent.

ethanol was boiled under a reflux condenser during 7 hours. The desired product of the reaction was isolated in a crude state according to the method described in Example 1, the final step being distillation up to a vapour temperature of 150° at 0.7 millimetres of mercury. The non-volatile residue consisting of crude 3 - methyl - 4 - 10^1 - bromodecyloxybenzonitrile (27.8 grammes) was dissolved in 130 millilitres of ethanol, treated with diethylamine (30 millilitres) and the solution boiled under a reflux condenser during 6 hours. After evaporation down to low bulk the basic part of the residue was isolated according to the method described in Example 1 and distilled at 0.001 millimetres of mercury. The fraction distilling between 185° and 225° (16.5 grammes) was 3 - methyl - 4 - 10^1 - diethylaminodecylbenzonitrile, which was pure enough for the present preparation. It was converted to the corresponding amidine, 3-methyl - 4 - 10^1 - diethylaminodecyloxybenzamidine, in the manner described in Example 1. The strongly alkaline product weighed 14.8 grammes and furnished 12.4 grammes of the sulphate salt, $C_{22}H_{39}N_3O,H_2O_4$, crystallising from 98 per cent. ethanol and melting at 215—219°.

EXAMPLE 7.

A solution of 6-hydroxy-2-naphthonitrile (12.7 grammes), sodium hydroxide (3.0 grammes) and 1:7 - dibromoheptane (41 grammes) in 350 millilitres of 90 per cent. ethanol was boiled under a reflux condenser during four hours. As in Example 1, the product was isolated, the final step being distillation up to a vapour temperature of 140° at 6.5 millimetres of mercury. The non-volatile residue consisting of crude 6-7^1-bromoheptyloxy - 2 - naphthonitrile (14.6 grammes), was dissolved in 100 millilitres of ethanol, treated with diethylamine (20 millilitres) and the solution boiled under a reflux condenser during 5 hours. By using methods described in Example 1, the solution furnished 6.7 grammes of 6 - 7^1 - diethylaminoheptyloxy - 2 - naphthonitrile hydrochloride which in its turn provided 5.8 grammes of 6 - 7^1 - diethylaminoheptyloxy - 2 - naphthamidine. The sulphate salt of this strongly alkaline substance has the formula $C_{22}H_{33}N_3O, H_2SO_4$. It is very soluble in water, crystallises from aqueous alcohol and melts at 258°—262°.

EXAMPLE 8.

Tablets of the following composition were prepared:

p - 10 - Diethylaminodecyloxybenzamidine sulphate	250 mg.
Starch	50 mg.
Magnesium stearate	2.5 mg.

The *p* - 10 - diethylaminodecyloxybenzamidine sulphate was powdered and mixed with the starch. The mixture was granulated with ethanol containing 10% of water, sifted through a sieve having 7.9 meshes/cm. and dried at 45°. The dried granules were sifted through a sieve having 7.9 meshes/cm. The magnesium stearate was added to and mixed with the dried granules. The mixture was compressed into tablets on a suitable tabletting machine.

The following examples were prepared by the method as described in Example 1.

Example No.	Name of amidine base	Empirical Formula of salt	Melting point of salt	Solvent from which the salt may be crystallized
9	*p*-6-diethylaminohexyloxybenzamidine	$C_{17}H_{29}N_3O,H_2SO_4$	249	water + methyl alcohol
10	*p*-7-diethylaminoheptyloxybenzamidine	$C_{18}H_{31}N_3O,H_2SO_4$	226 — 231	water + ethyl alcohol
11	*p*-8-diethylaminooctyloxybenzamidine	$C_{19}H_{33}N_3O,H_2SO_4$	221 — 227	water + ethyl alcohol
12	*p*-9-diethylaminononyloxybenzamidine	$C_{20}H_{35}N_3O,H_2SO_4$	231 — 233	water + ethyl alcohol
13	*p*-12-diethylaminododecyloxybenzamidine	$C_{23}H_{41}N_3O,H_2SO_4$	224 — 227	water + ethyl alcohol
14	*p*-7-ethylaminoheptyloxybenzamidine	$C_{16}H_{27}N_3O,H_2SO_4$	271	water + ethyl alcohol
15	*p*-7-*n*-propylaminoheptyloxybenzamidine	$C_{17}H_{29}N_3O,H_2SO_4$	279 — 287	5 per cent. aqueous sulphuric acid
16	*p*-7-di-*n*-propylaminoheptyloxybenzamidine	$C_{20}H_{35}N_3O,H_2SO_4$	ca. 200	methyl + ethyl alcohols
17	*p*-7-*n*-butylaminoheptyloxybenzamidine	$7C_{18}H_{31}N_3O,H_2SO_4$	280 — 287	2.5 per cent aqueous sulphuric acid
18	*p*-7-*iso*-butylaminoheptyloxybenzamidine	$7C_{18}H_{31}N_3O,H_2SO_4$	280 — 285	5 per cent. aqueous sulphuric acid
19	*p*-7-piperidinoheptyloxybenzamidine	$C_{19}H_{31}N_3O,H_2SO_4$	270 — 273	water + ethyl alcohol
20	*p*-7-morpholinoheptyloxybenzamidine	$C_{18}H_{29}N_3O_2,H_2SO_4$	229 — 233	water + ethyl alcohol
21	*p*-8-dimethylaminooctyloxybenzamidine	$C_{17}H_{29}N_3O,H_2SO_4$	215 — 220	water + ethyl alcohol
22	*p*-8-allylaminooctyloxybenzamidine	$C_{18}H_{29}N_3O,H_2SO_4$	218 — 223	water + ethyl alcohol
23	*p*-8-di-*n*-butylaminooctyloxybenzamidine	$C_{23}H_{41}N_3O,H_2SO_4$	160 — 165	water + ethyl alcohol
24	*p*-8-piperazinooctyloxybenzamidine	$C_{19}H_{32}N_4O,1.5H_2SO_4$	241 — 253	water + methyl alcohol
25	*p*-8-N^1-benzhydrylpiperazinooctyloxybenzamidine	$C_{32}H_{42}N_4O,1.5H_2SO_4$	indefinite	water + methyl alcohol

Example No.	Name of amidine base	Empirical Formula of salt	Melting point of salt	Solvent from which the salt may be crystallized
26	3-methyl-4-8¹-diethylaminooctyloxybenzamidine	$C_{20}H_{35}N_3O,H_2SO_4$	238—243	85% ethanol
27	3-methyl-4-9¹-diethylaminononyloxybenzamidine	$C_{21}H_{37}N_3O,H_2SO_4$	223—227	Methanol
28	6-10¹-diethylaminodecyloxy-2-naphthamidine	$C_{25}H_{39}N_3O,H_2SO_4$	232—234	90% ethanol
29	3-chloro-4-8¹-diethylaminooctyloxybenzamidine	$C_{19}H_{32}ClN_3O,H_2SO_4$	199—202	Moist ethanol
30	3-chloro-4-9¹-diethylaminononyloxybenzamidine	$C_{20}H_{34}ClN_3O,H_2SO_4$	210—213 (this m.p. is much affected by hydration)	Moist ethanol
31	3-bromo-4-10¹-diethylaminodecyloxybenzamidine	$C_{21}H_{36}BrN_3O,H_2SO_4$	179—185	98% ethanol
32	3-methoxy-4-7¹-diethylaminoheptyloxybenzamidine	$C_{19}H_{33}N_3O_2,H_2SO_4$	262—270	Aqueous Ethoxyethanol
33	3-methoxy-4-8¹-diethylaminooctyloxybenzamidine	$C_{20}H_{35}N_3O_2,H_2SO_4$	219—222	Moist ethanol
34	3-methoxy-4-9¹-diethylaminononyloxybenzamidine	$C_{21}H_{37}N_3O_2,H_2SO_4$	223—228	Moist ethanol
35	3-methoxy-4-10¹-diethylaminodecyloxybenzamidine	$C_{22}H_{39}N_3O_2,H_2SO_4$	227—233	Mixture of methanol and ethanol
36	*p*-10-Dimethylaminodecyloxybenzamidine	$C_{19}H_{33}N_3O,H_2SO_4$	186—192	85% Methanol
37	*p*-10-Ethylaminodecyloxybenzamidine	$C_{19}H_{33}N_3O,H_2SO_4$	194—200	80% Methanol
38	*p*-10-Di-*n*-propylaminodecyloxybenzamidine	$C_{23}H_{41}N_3O,H_2SO_4$	181—186	Mixture of Methanol (1) and Ethanol (3)
39	*p*-10-Pyrrolidinodecyloxybenzamidine	$C_{21}H_{35}N_3O,H_2SO_4$	215—228	60% Ethanol
40	*p*-10-Morpholinodecyloxybenzamidine	$C_{21}H_{35}N_3O_2,H_2SO_4$	160—178	75% Ethanol
41	3:5-Dimethyl-4:10¹-diethylaminodecyloxybenzamidine	$C_{23}H_{41}N_3O,2HCl$	160—165	Moist Acetone

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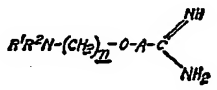
WHAT WE CLAIM IS:—

1. A compound of the general formula:



and acid addition salts thereof, wherein R^1 and R^2 are the same or different and each is a hydrogen atom or an aliphatic hydrocarbon radical containing from 1 to 4 carbon atoms, or the group R^1R^2N— is a piperidino, pyrrolidino, morpholino, piperazino, or N^1-benzhydrylpiperazino group; n is an integer from 7 to 12; and A is an arylene group and is a 1:4-phenylene group which may be substituted in the positions *ortho* with respect to the alkyleneoxyl chain with a methyl or methoxyl group or a halogen atom, or is a 2:6-naphthylene group.

2. A compound as defined in Claim 1 as a sulphuric acid addition salt.

3. *p* - 10 - Diethylaminodecyloxybenzamidine and acid addition salts thereof.

4. 3 - Methyl - 4 - 10^1 - diethylaminodecyloxybenzamidine and acid addition salts thereof.

5. 6 - 7^1 - Diethylaminoheptyloxy - 2-naphthamidine and acid addition salts thereof.

6. A method for the preparation of a compound of the formula defined in claim 1, wherein an aminoalkoxyarylene nitrile of the formula:

$$R^1R^2N—(CH_2)_n—O—A—CN$$

wherein R^1 R^2, n and A are as defined in Claim 1, is converted to the corresponding aminoalkoxyarylene amidine by any known method for converting a cyano to an amidino group.

7. A method as claimed in Claim 6 wherein the aminoalkoxyarylene nitrile is converted to the aminoalkoxyarylene amidine by the reaction with an alcohol to give an imino ether, followed by the reaction of the latter with ammonia or an ammonium salt.

8. A method as claimed in Claim 6 wherein the aminoalkoxyarylene nitrile is converted to the aminoalkoxyarylene amidine by the reaction with ammonium thiocyanate or an ammonium arenesulphonate in the presence of ammonia.

9. A method as claimed in Claim 6 wherein the aminoalkoxyarylene nitrile is converted to the aminoalkoxyarylene amidine by the reaction with an alkali metal amide in the presence of ammonia.

10. A method as claimed in Claim 6 wherein the aminoalkoxyarylene nitrile is converted to the aminoalkoxyarylene amidine by the reaction with ammonia or urea in the presence of an inorganic condensing agent.

11. A method for the preparation of a compound of the formula defined in Claim 1, substantially as herein described with reference to any one of the foregoing examples.

12. A compound of the formula defined in Claim 1 when prepared by any of the methods substantially as hereinbefore described or ascertained or any obvious chemical equivalent thereof.

13. A pharmaceutical preparation comprising an aminoalkoxyarylene amidine or its acid addition salt as defined in Claim 1 together with an acceptable carrier therefor.

14. A method for the preparation of a pharmaceutical preparation as defined in Claim 13 by the admixture of a compound as defined in claim 1 with an acceptable carrier therefor.

R. F. HASLAM,
Agent for the Applicants.

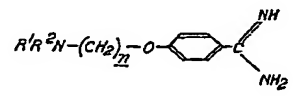
PROVISIONAL SPECIFICATION
No. 37608 A.D. 1957

Improvements in or relating to Novel Amidines and the preparation thereof

We, THE WELLCOME FOUNDATION LIMITED, a British Company, of 183—193, Euston Road, London, N.W.1, do hereby declare this invention to be described in the following statement:—

The present invention relates to novel amidines and the preparation thereof.

According to the present invention there are provided novel amidines of the general formula (I) and their acid addition salts.



(I)

In this and succeeding formulae:—

R^1 and R^2 are identical or different and are hydrogen or aliphatic hydrocarbon radicals containing from 1 to 6 carbon atoms, or

the group R^1R^2N— is a piperidino, pyrrolidino, morpholino, piperazino, or N^1 - benzhydrylpiperazino group; and

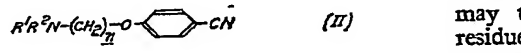
n is an integer from 6 to 14.

These compounds are found to be valuable as therapeutic agents, particularly as amoebicides.

Compounds of formula (I) may be prepared by a number of synthetic routes and methods which are all well understood in the art and any such methods may be employed in the

preparation of compounds of the present invention.

According to an aspect of the present invention, the compounds of formula (I) are prepared by converting the cyano group of a compound of the general formula (II) into an amidine group, by methods well known *per se* for such a conversion.



(II)

For example the cyano group may be converted to an amidine group by reaction of a compound of formula (II) with an alcohol to give an imino ether, followed by the reaction of the latter with ammonia or an ammonium salt.

Another method of conversion comprises for example the reaction of a compound of formula (II) with ammonium thiocyanate or aryl sulphonate (such as the benzene sulphonate) in the presence of ammonia.

The conversion may also take place by the reaction of a compound of formula (II) with sodamide in the presence of ammonia.

In another method a compound of formula (II) is reacted with ammonia or urea in the presence of an inorganic condensing agent such as aluminium chloride, zinc chloride, ferric chloride or stannic chloride.

In the full synthesis of the compounds of the present invention, the sodium salt of *p*-hydroxybenzonitrile is condensed with an excessive proportion of an $\alpha:\omega$-alkylene dibromide and the resulting ω-bromoalkoxybenzonitrile (which may be largely separated from the $\alpha:\omega$-bis-*p*-cyanophenoxyalkane which is also formed by taking advantage of its relatively great solubility in ether) can be brought into reaction with an amine of the formula R^1R^2NH. The resulting ω-amino-, or substituted ω-aminoalkoxybenzonitrile may then be converted into the corresponding amidine by any one of the methods known *per se* as described above. Usually, the product is best obtained in the form of its sulphate salt.

The invention will now be described by reference to the following Examples.

EXAMPLE 1.

A solution of one molecular equivalent of *p*-hydroxybenzonitrile (110 grammes) in a mixture of alcohol (2250 millilitres) and water (350 millilitres) is treated with one molecular equivalent of sodium hydroxide (36.9 grammes) and 1.99 molecular equivalents of 1:10-dibromodecane (550 grammes) and boiled under a reflux condenser during 6 hours. After removing nearly all the alcohol on a steam-bath under diminished pressure, the residue is treated with water and extracted with 3 litres of ether. The extract is dried over anhydrous sodium sulphate, and, upon removing the solvent by evaporation, furnishes a residue which may be subjected to distillation at a pressure of 2.5 millimetres of mercury until the vapour temperature rises to 200°. The resulting distillate, which contains the unreacted excess of the decamethylene dibromide together with products derived therefrom by condensation with the reaction medium, serves for the regeneration and recovery of decamethylene dibromide which may then be used again. The distillation residue which is a solid material weighing 201 grammes is found by elementary analysis to contain 20.2 per cent of bromine. It contains the *p*-10-bromodecyloxybenzonitrile, which is the main product of the operation, as well as some 1:10-bis-*p*-cyanophenoxydecane which is also formed. The latter substance is a solid, sparingly soluble in ether and insoluble in an aqueous medium; while the greater part of it is out of solution and may be filtered out before or during the ether extraction (or it may be ignored), some, nevertheless, finds its way into the ethereal extract and of this, some is deposited on the drying agent and may be filtered out with it. But some proportion of this compound is always found dissolved in the dried ethereal liquid and is for this reason present as an impurity in the *p*-10-bromodecyloxybenzonitrile prepared as described above. However, for the purpose of this invention, the material which weighs 201 grammes and contains 20.2 per cent of bromine is sufficiently pure and may be submitted to the next stage of the process in the condition described. For this purpose it may be dissolved in alcohol (500 c.c.), treated with diethylamine (100 c.c.) and this solution boiled under a reflux condenser during 6 hours. The only basic substance formed in this reaction is that produced by the condensation of the diethylamine with the *p*-10-bromodecyloxybenzonitrile. The impurity aforementioned does not react and is not basic in character; it may therefore now be eliminated by methods which are well understood. Thus, after evaporating most of the alcohol and unreacted excess of diethylamine upon a steam-bath under diminished pressure, the residue is treated with water, with an excess of a solution of a caustic alkali and is extracted with one and one-half litres of ether. The product of the reaction, *p*-10-diethylaminodecyloxybenzonitrile, is withdrawn from the ethereal solution by means of dilute aqueous hydrochloric acid. (The remaining ethereal solution so bereft of its basic solute furnishes 34 grammes of a non-basic impurity). The *p*-10-diethylaminodecyloxybenzonitrile hydrochloride now present in dilute aqueous acid solution may be crystallised forthwith, or, it may be further purified by a renewed transference to ether with the aid of an alkali followed by a return to aqueous hydrochloric acid; or, it may be purified in the condition of base by a process of distillation

in a vacuum when a small amount of a higher boiling impurity may be eliminated. The *p*-10 - diethylaminodecyloxybenzonitrile hydrochloride so obtained is finally recrystallised from acetone when it constitutes a white crystalline solid weighing 18.5 grammes and melting at 75—85°. It is very soluble in water, in the common alcohols and in hot but not in cold acetone.

Throughout the succeeding operations, during which the nitrile just described is converted to the corresponding amidine, rigorously anhydrous conditions (achieved with the aid of well-known and customary devices) are observed.

A solution of dry *p*-10-diethylaminodecyloxybenzonitrile hydrochloride (95 grammes) in absolute ethyl alcohol (100 millilitres) is placed in a trough of water (so as to prevent the temperature from rising above about 20°) and saturated with dry hydrogen chloride gas. After standing for 24 hours at the temperature of the room, all volatile matter is removed by suction, the temperature being prevented from falling unduly by immersion in a trough of water at 20°. The residue, which is a gum weighing 130 grammes and showing an incipient tendency to crystallise, is dissolved in 100 millilitres of absolute ethyl alcohol, cooled to a temperature of +5° and mixed with 400 millilitres of a solution (whose temperature is likewise at +5°) obtained by saturating absolute ethyl alcohol kept at 20° with anhydrous ammonia gas. The resulting liquid, which contains a white crystalline solid uniformly suspended therein, is saturated with dry ammonia gas under the conditions already prescribed. After standing at 20° for 65 hours, nearly all volatile matter is removed by suction at 20°. The residue is then treated with 2½ litres of water charged with a large excess of a caustic alkali and extracted with one litre of ether. After drying over a suitable drying agent such as anhydrous sodium sulphate, most of (but not all) the ether is removed from the filtered liquid by evaporation upon a steam-bath. Complete elimination of the solvent is achieved at room temperature by suction under suitable conditions: it is of course not now necessary to observe in all rigour the fully anhydrous conditions hitherto imperative, but suitable precautions are nevertheless taken to prevent an excessive amount of dew being deposited upon the product at this stage. In this way there is obtained a soft, white, crystalline solid which weighs 95 grammes. It is converted to the sulphate salt whose composition is $C_{21}H_{37}N_3O,H_2SO_4$ by means of a suitable solution containing 25.5 grammes of H_2SO_4. This salt is crystallised and may be recrystallised from a mixture of water (40 millilitres) and absolute ethyl alcohol (300 millilitres). The first crop weighs 92 grammes, and a further 25 grammes of not greatly inferior material can be recovered from the mother-liquor in a series of additional crops. The salt melts at 224—229° with decomposition. It is very soluble in water but almost insoluble in dry alcohol and other organic solvents.

EXAMPLE 2.

p - 10 - Diethylaminodecyloxybenzonitrile hydrochloride, prepared according to the method described in Example 1, (1.5 g.), and ammonium thiocyanate (1.5 g.) are melted together and heated with stirring to 150° while a stream of dry ammonia is passed in. The temperature is then raised to 180° and maintained for 2 hours. The product is shaken with water, sodium hydroxide and ether, the ether removed and the residue dissolved in absolute alcohol and converted to sulphate with dilute sulphuric acid. *p*-10-Diethylaminodecyloxybenzamidine sulphate crystallizes, melting point 228—9°, identical with the compound described in Example 1.

EXAMPLE 3.

p - 10 - Diethylaminodecyloxybenzonitrile benzene sulphonate (2.5 g.) and ammonium benzene sulphonate (2.5 g.) are heated and stirred in a current of dry ammonia for 4 hours at 200°. The product is extracted with 30 c.c. of hot water and after cooling filtered from some unreacted *p*-10-diethylaminodecyloxybenzonitrile benzene sulphonate. The aqueous filtrate is made alkaline with sodium hydroxide solution and extracted with ether. The ether is evaporated and the residue converted to sulphate as in Example 1. *p*-10-Diethylaminodecyloxybenzamidine sulphate is obtained in white crystals melting point 230° identical with the product obtained in Example 1.

EXAMPLE 4.

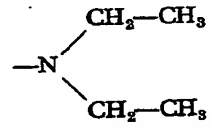
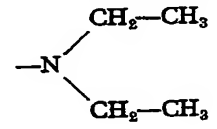
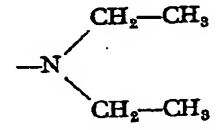
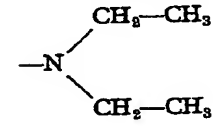
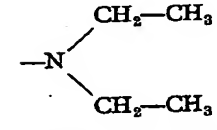
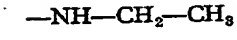
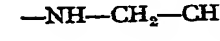
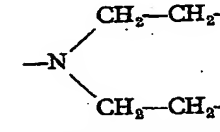
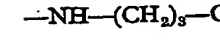
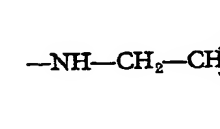
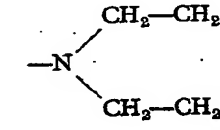
To *p* - 10 - diethylaminodecyloxybenzonitrile (2.2 g.) in dry xylene (10 c.c.) is added sodamide (2.6 g.) finely powdered under xylene (10 c.c.). The mixture is stirred and boiled under reflux for 6 hours in a stream of dry ammonia. The product which consists of a gelatinous suspension is poured into water; it forms a milky liquid which is acidified with dilute hydrochloric acid. The liquid clears forming two layers which are separated. The aqueous layer is basified with sodium hydroxide and extracted with ether. The ether on evaporation leaves behind *p*-10-diethylaminodecyloxybenzamidine which is characterized by conversion to the sulphate melting point 228—9°.

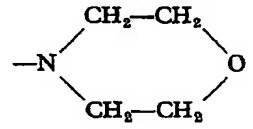
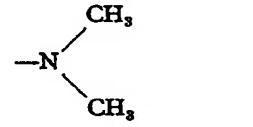
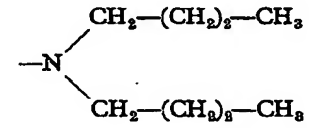
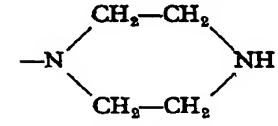
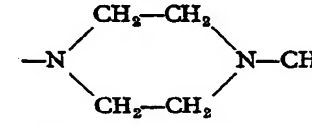
EXAMPLE 5.

p - 10 - Diethylaminodecyloxybenzonitrile hydrochloride (1.9 g.) is mixed with urea (11.4 g.) and heated in an oil-bath to 150°; anhydrous aluminium chloride (0.67 g.) is then added in portions. A vigorous reaction takes place and when this has subsided the temperature is raised to 190° for one and a half hours. On cooling a horny mass is obtained which is converted to a milky suspension with 150 c.c. of hot water. The suspension is acidified,

centrifuged to remove aluminium compounds, made alkaline and extracted with ether to obtain the *p*-10-diethylaminodecyloxybenzamidine, characterised by conversion to sulphate melting point 227—230° and identical with that obtained in Example 1.

The following compounds shown in the following table may be prepared in an analogous manner.

Example No.	R^1R^2N—	*n*	Formula of Salt	Melting point of salt °C.	Solvent from which the salt may be crystallised
6		6	$C_{17}H_{29}N_3O_3H_2SO_4$	249	water + methyl alcohol
7		7	$C_{18}H_{31}N_3O_3H_2SO_4$	226 — 231	water + ethyl alcohol
8		8	$C_{19}H_{33}N_3O_3H_2SO_4$	221 — 227	water + ethyl alcohol
9		9	$C_{20}H_{35}N_3O_3H_2SO_4$	231 — 233	water + ethyl alcohol
10		12	$C_{23}H_{41}N_3O_3H_2SO_4$	224 — 227	water + ethyl alcohol
11		7	$C_{16}H_{27}N_3O_3H_2SO_4$	271	water + ethyl alcohol
12		7	$C_{17}H_{29}N_3O_3H_2SO_4$	279 — 287	5 per cent. aqueous sulphuric acid
13		7	$C_{20}H_{35}N_3O_3H_2SO_4$	ca. 200	methyl + ethyl alcohols
14		7	$C_{18}H_{31}N_3O_3H_2SO_4$	280 — 287	2.5 per cent. aqueous sulphuric acid
15		7	$C_{18}H_{31}N_3O_3H_2SO_4$	280 — 285	5% aqueous sulphuric acid
16		7	$C_{19}H_{31}N_3O_3H_2SO_4$	270 — 273	water + ethyl alcohol

Example No.	R^1R^2N—	n	Formula of Salt	Melting point of salt °C.	Solvent from which the salt may be crystallised
17		7	$C_{18}H_{29}N_3O_2,H_2SO_4$	229 — 233	water + ethyl alcohol
18		8	$C_{17}H_{29}N_3O_2,H_2SO_4$	215 — 220	water + ethyl alcohol
19	—NH—CH_2.CH:CH_2	8	$C_{18}H_{29}N_3O_2,H_2SO_4$	218 — 223	water + ethyl alcohol
20		8	$C_{23}H_{41}N_3O,H_2SO_4$	160 — 165	water + ethyl alcohol
21		8	$C_{19}H_{32}N_4O,1.5H_2SO_4$	241— 253	water + methyl alcohol
22		8	$C_{32}H_{42}N_4O,1.5H_2SO_4$	indefinite	water + methyl alcohol

These sulphates are characterised by their insolubility in the dry alcohols, especially in absolute ethyl alcohol. The sulphates of those substances in which R^1R^2N— is a tertiary amino-group are very soluble in water and have relatively lower melting points. The sulphates of those substances in which R^1R^2N— is a secondary amino-group have higher melting points and are less soluble, in some cases quite sparingly soluble, in water.

R. F. HASLAM,
Agent for the Applicants.

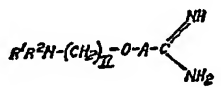
PROVISIONAL SPECIFICATION
No. 30546 A.D. 1958

Improvements in or relating to Novel Amidines and the preparation thereof

We, THE WELLCOME FOUNDATION LIMITED, a British Company, of 183—193, Euston Road, London, N.W.1, do hereby declare this invention to be described in the following statement: —

In copending application, No. 37,608/57 there are described some novel amidines and the preparation thereof. These compounds are found to be valuable as therapeutic agents, particularly as amoebicides. The present invention relates to a further group of novel amidines and the preparation thereof, this further group also having value as therapeutic agents, particularly as amoebicides.

According to the present invention there are provided novel amidines of the general formula (I) and their acid addition salts.



(I)

In this and succeeding formulae: —

R^1 and R^2 are identical or different and are hydrogen or aliphatic hydrocarbon radicals con-

taining from 1 to 4 carbon atoms, or

the group R^1R^2N— is a piperidino, pyrrolidino, morpholino, piperazino, or N^1-benzhydrylpiperazino group;

n is an integer from 7 to 12; and

A is an arylene group and is a 1,4-phenylene group substituted in the *ortho*-position with respect to the alkyleneoxyl chain with a methyl or methoxyl group or a halogen atom, or is a 2,6-naphthylene group.

Compounds of formula (I) may be prepared by a number of synthetic routes and methods which are all well understood in the art and any such method may be employed in the preparation of compounds of the present invention.

According to an aspect of the present invention, the compounds of formula (I) are prepared by converting the cyano group of a compound of the general formula (II) into an amidine group, by methods well known *per se* for such a conversion.

$$R^1R^2N-(CH_2)_n-O-A-CN \qquad (II)$$

For example the cyano group may be converted to an amidine group by reaction of a compound of formula (II) with an alcohol to give an imino ether, followed by the reaction of the latter with ammonia or an ammonium salt.

Another method of conversion comprises the reaction of a compound of formula (II) with ammonium thiocyanate or an ammonium aryl sulphonate (such as the benzene sulphonate) in the presence of ammonia.

The conversion may also take place by the reaction of a compound of formula (II) with sodamide in the presence of ammonia.

In another method a compound of formula (II) is reacted with ammonia or urea in the presence of an inorganic condensing agent such as aluminium chloride, zinc chloride, ferric chloride or stannic chloride.

In the full synthesis of the compounds of the present invention, the sodium salt of a hydroxy nitrile of the formula HO—A—CN is condensed with an excessive proportion of an $\alpha:\omega$-alkylene dibromide and the resulting ω-bromoalkoxy nitrile (which may be largely separated from the $\alpha:\omega$ - bis - *p* - *cyano*-aryleneoxyalkane which is also formed by taking advantage of its relatively greater solubility in ether) can be brought into reaction with an amine of the formula R^1R^2NH. The ω-amino-, or substituted ω-aminoalkoxy nitrile produced may then be converted into the corresponding amidine which is the desired product by any of the methods known *per se* as described above. Usually the product is best obtained in the form of its sulphate salt.

The invention will now be described by reference to the following Examples, in which all temperatures are given in degrees Centigrade.

EXAMPLE 1.

A solution of 3-methyl-4-hydroxybenzonitrile (13.3 grammes), sodium hydroxide (4.0 grammes) and 1:10 dibromodecane (60.0 grammes) in 440 millilitres of 86 per cent. ethanol was boiled under a reflux condenser during 7 hours. The desired product of the reaction was isolated in a crude state in the manner described for an analogous case in Example 1 of co-pending application, No. 37608/57, *viz.* by evaporation, dilution, filtration and removal of the extraneous volatile fraction from the ether-soluble part of the resulting material by distillation up to a vapour temperature of 150° at 0.7 millilitres of mercury. The non-volatile residue consisting of crude 3 - methyl - 4 - 10^1 - bromodecyloxybenzonitrile (27.8 grammes) was dissolved in 130 millilitres of ethanol, treated with diethylamine (30 millilitres) and the solution boiled under a reflux condenser during 6 hours. After evaporation down to low bulk the basic part of the residue was isolated in the well known manner for such operations described in Example 1 of co-pending application, No. 37608/57 and distilled at 0.001 millimetres of mercury. The fraction distilling between 185° and 225° (16.5 grammes) was 3-methyl-4 - 10^1 - diethylaminodecyloxybenzonitrile, which was pure enough for the present preparation. It was converted to the corresponding amidine, 3 - methyl - 4 - 10^1 - diethylaminodecyloxybenzamidine, in the manner described in Example 1 of co-pending application, No. 37608/57. The strongly alkaline product weighed 14.8 grammes and furnished 12.4 grammes of the sulphate salt, $C_{22}H_{39}N_3O,H_2SO_4$, crystallising from 98 per cent. ethanol and melting at 215—219°.

EXAMPLE 2.

A solution of 6-hydroxy-2-naphthonitrile (12.7 grammes), sodium hydroxide (3.0 grammes) and 1:7 - dibromoheptane (41 grammes) in 350 millilitres of 90 per cent. ethanol was boiled under a reflux condenser during four hours. As in Example 1 of co-pending application No. 37608/57, the product was isolated, the final step being distillation up to a vapour temperature of 140° at 6.5 millimetres of mercury. The non-volatile residue consisting of crude 6-7^1-bromoheptyloxy - 2 - naphthonitrile (14.6 grammes), was dissolved in 100 millilitres of ethanol, treated with diethylamine (20 millilitres) and the solution boiled under a reflux condenser during 5 hours. By using methods described in Example 1 of co-pending application, No. 37608/57, the solution furnished 6.7 grammes of 6 - 7^1-diethylaminoheptyloxy - 2 - naphthonitrile hydrochloride which in its turn provided 5.8 grammes of 6 - 7^1 - diethylaminoheptyloxy-

2-naphthamidine. The sulphate salt of this strongly alkaline substance has the formula $C_{22}H_{33}N_3O,H_2SO_4$. It is very soluble in water, crystallises from aqueous alcohol and melts at 258°—262°.

The compounds shown in the following table may be prepared in an analogous manner:—

Example No.	Name of amidine base	Empirical Formula of salt	Melting Point of salt	Solvent from which the salt may be crystallized
3	3-methyl-4-8¹-diethylaminooctyloxybenzamidine	$C_{20}H_{35}N_3,H_2SO_4$	238—243	85% ethanol
4	3-methyl-4-9¹-diethylaminononyloxybenzamidine	$C_{21}H_{37}N_3O,H_2SO_4$	223—227	Methanol
5	6-10¹-diethylaminodecyloxy-2-naphthamidine	$C_{28}H_{39}N_3O,H_2SO_4$	232—234	90% ethanol
6	3-chloro-4-8¹-diethylaminooctyloxybenzamidine	$C_{19}H_{32}ClN_3O,H_2SO_4$	199—202	Moist ethanol
7	3-chloro-4-9¹-diethylaminononyloxybenzamidine	$C_{20}H_{34}ClN_3O,H_2SO_4$	210—213 (this m.p. is much affected by hydration)	Moist ethanol
8	3-bromo-4-10¹-diethylaminodecyloxybenzamidine	$C_{21}H_{36}BrN_3O,H_2SO_4$	179—185	98% ethanol
9	3-methoxy-4-7¹-diethylaminoheptyloxybenzamidine	$C_{19}H_{33}N_3O_2,H_2SO_4$	262—270	Aqueous Ethoxyethanol
10	3-methoxy-4-8¹-diethylaminooctyloxybenzamidine	$C_{20}H_{35}N_3O_2,H_2SO_4$	219—222	Moist ethanol
11	3-methoxy-4-9¹-diethylaminononyloxybenzamidine	$C_{21}H_{37}N_3O_2,H_2SO_4$	223—228	Moist ethanol
12	3-methoxy-4-10¹-diethylaminodecyloxybenzamidine	$C_{22}H_{39}N_3O_2,H_2SO_4$	227—233	Mixture of methanol and ethanol

These sulphates are characterised by their insolubility in the dry alcohols, especially in absolute ethyl alcohol. The sulphates of those substances in which R^1R^2N— is a tertiary amino-group are very soluble in water and have relatively lower melting points. The sulphates of those substances in which R^1R^2N— is a secondary amino-group have higher melting points and are less soluble, in some cases quite sparingly soluble, in water.

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